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EORTC Brain Tumor Group

Trabectedin for recurrent grade II or III meningioma: a randomized phase II study of the EORTC Brain Tumor Group

EORTC protocol 1320-BTG

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Study Coordinator: Matthias Preusser

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Protocol 1320

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Protocol summary

Title of the Study	Trabectedin for recurrent grade II or III meningioma: a randomized phase II study of the EORTC Brain Tumor Group
Objective(s)	The aim of this randomized phase II study is to collect data on activity, safety and quality of life of trabectedin therapy in patients with recurrent high-grade meningioma.
Methodology	Phase II, 2:1 randomization, Korn design
Number of patients Number planed (Statistical design) Number analyzed	Total number of patients: 86 eligible patients who started allocated treatment (57 in the experimental arm, 29 in the control arm). With 2:1 randomization and assuming 6-month progression-free survival (PFS-6)=15% in the control and 35% in the trabectedin arm, assuming PFS follows an exponential distribution, Hazard Ratio (HR)=0.55, one-sided logrank test, at alpha=10% (20% two sided), power=85%, 72 progression or death events are needed to assess the targeted effect. 86 eligible patients who started allocated treatment will be analyzed (57 trabectedin, 29 control). Assuming an accrual of 7.17 patients per month (1.99 months 0-4, 3.55 months 4-8, 5.29 months 8-12 and 7.17 beyond 12 months), about 18 months of recruitment are needed.
Diagnosis and main criteria for inclusion	♦ Age 18 or older ♦ Histological diagnosis of WHO grade II (chordoid meningioma, clear cell meningioma, atypical meningioma) or WHO grade III (papillary meningioma, rhabdoid meningioma, anaplastic/malignant meningioma) according to WHO 2007 classification. ♦ Radiologically documented progression of any existing tumor (growth > 25% in the last year) or appearance of new lesions (including intra- and extracranial manifestations) ♦ No more option for local therapy (resection or radiotherapy) after maximal feasible surgery and radiotherapy ♦ No prior systemic anti-neoplastic therapy for meningioma (patient may have received prior radionuclide therapy) ♦ Measurable disease (10 x10 mm) on cranial MRI no more than 2 weeks prior to randomization ♦ WHO performance status 0-2 ♦ Adequate liver, renal and hematological function within 2 weeks prior to randomization, defined as: ♦ Neutrophils ≥ 1.5 x 10^9/L, hemoglobin ≥ 9 g/dL or hemoglobin ≥ 5.6 mmol/L, platelets ≥ 100 x 10^9/L ♦ Total Bilirubin ≤ 1 x ULN, SGPT/ALT and SGOT/AST ≤ 2.5 x ULN ♦ Alkaline phosphatase ≤ 2.5 x ULN; if alkaline phosphatase > 2.5 ULN, hepatic isoenzymes 5-nucleotidase or gamma

	glutyamyltransferase (GGT) must be within the normal range ♦ Albumin ≥ 30 g/L ♦ Serum creatinine ≤ 1.5 x ULN ♦ Creatinine clearance > 30 ml/min as calculated by Cockcroft and Gault formula (see Appendix E) ♦ Creatine phosphokinase (CPK) ≤ 2.5 x ULN ♦ Normal cardiac function (LVEF assessed by MUGA or ECHO within normal range of the institution), normal 12 lead ECG (without clinically significant abnormalities). The following unstable cardiac conditions are not allowed: ♦ Congestive heart failure ♦ Angina pectoris ♦ Myocardial infarction within 1 year before registration/randomization ♦ Uncontrolled arterial hypertension defined as blood pressure ≥ 150/100 mm Hg despite optimal medical therapy ♦ Arrhythmias clinically significant ♦ Life expectancy of at least 9 weeks ♦ No history of any other invasive malignancy within the last 5 years (except adequately treated non-melanoma skin cancer, clinically localized and very low risk prostate cancer, and adequately treated cervical intraepithelial neoplasia) ♦ No serious illness or medical conditions, specifically: active infectious process; chronic active liver disease, including chronic hepatitis B, C or cirrhosis ♦ No concomitant use of any other investigational agent, phenytoin, or vaccination to yellow fever. ♦ Women of child bearing potential (WOCBP) must have a negative serum (or urine) pregnancy test within 72 hours prior to randomization (and again within 72 hours prior to the first dose of study treatment). Patients of childbearing / reproductive potential should use adequate birth control measures, as defined below, during the study treatment period and for at least 3 months after the last study treatment. Men who are fertile must use effective contraception during treatment with trabectedin and for 5 months thereafter. Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include: ♦ combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: ♦ oral ♦ intravaginal

	♦ transdermal ♦ progestogen-only hormonal contraception associated with inhibition of ovulation: ♦ oral ♦ injectable ♦ implantable ♦ intrauterine device (IUD) ♦ intrauterine hormone-releasing system (IUS) ♦ bilateral tubal occlusion ♦ vasectomised partner ♦ sexual abstinence ♦ Acceptable birth control methods that result in a failure rate of more than 1% per year include: ♦ progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action ♦ male or female condom with or without spermicide ♦ cap, diaphragm or sponge with spermicide ♦ Female subjects who are breast feeding should discontinue nursing prior to the first dose of study treatment and until 3 months after the last study treatment. ♦ No known hypersensitivity or contraindication to trabectedin or any of the ingredients of the trabectedin solution for infusion ♦ No known MRI or CT, including contrast media, contraindications ♦ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial ♦ Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.
Treatment Test product, dose and mode of administration	Trabectedin will be delivered as a 24-hour infusion every 3 weeks (day 1 of each 21-day cycle) at a starting dose of 1.5 mg/m^2 BSA. Administration through a central venous line is strongly recommended. Subjects receiving trabectedin are required to receive dexamethasone pretreatment at 20 mg IV, 30 minutes before starting trabectedin.
Duration of treatment	Until progression or unacceptable toxicity or patients' refusal.

Reference therapy, dose and mode of administration	Local standard of care
Criteria for evaluation	Primary end-point: Progression Free Survival (PFS) Secondary end-points: ♦ Progression Free Survival at 6 months (PFS-6), median PFS (mPFS) ♦ Best overall response (BOR). Objective response (CR/PR), rate and median duration. Complete response (CR), rate and median duration. ♦ Overall survival (OS), OS probability at 6 (OS6) and 12 months (OS12), median OS (mOS) ♦ Safety (CTCAE v.4.0) ♦ Health-related Quality of life (HRQol)
Statistical methods	The primary endpoint, PFS, will be compared between the trabectedin and the control arm when 71 PFS events are observed. A Cox regression model adjusted by stratification factors at randomization (except institution) will be fit. If Proportional Hazards assumptions (PH) are not respected (as assessed by Schoenfeld residuals) for a particular factor, the model will be stratified and not adjusted by this factor. The superiority of trabectedin against the control arm will be tested at 10% one-sided (20% two-sided) significance level. The treatment Hazard Ratio (HR) estimate will be presented with 90% one-sided confidence interval (CI). 95% CI will also be presented. The PFS-6 and the mPFS will be extracted from the Kaplan-Meyer PFS curve. 95% confidence intervals will be computed based on the Greenwood's formula. For the median the Reflected Method will provide 95% confidence intervals.

Translational research	Formalin-fixed, paraffin-embedded (FFPE) blocks of tumor samples will be collected for retrospective central pathology review. In addition, the association of tumor proliferation, microvascular density, and density of tumor-associated macrophages with response to treatment will be explored using immunohistochemistry. In addition, the full landscape of potential diagnostic, prognostic and predictive molecular markers within the tumor samples will be profiled by means of next-generation-sequencing and the Illumina 850k methylation assay. Retrospective review of the images will take place for this study. Although treatment decisions are based on objective tumor assessment at the treating sites, retrospective central review will reassess all images to confirm the initial assessment. Retrospective studies have indicated that systemic therapy may decrease the growth rate of meningiomas. MRI scans acquired up to 2 years before inclusion of patients into the EORTC-1320 trial will be collected to investigate whether the growth dynamics of grade II or III meningiomas changes with start of study treatment. Preliminary response assessment in neuro-oncology (RANO) criteria for response assessment in meningioma were presented in the RANO working group meeting during the 2014 ASCO annual meeting. Publication is expected. 2D and volumetric measurements will be obtained through retrospective imaging review, aiming to add information towards validation of the RANO response assessment criteria for meningioma.
Quality of Life	The main objective of HRQoL assessment within this trial is to determine the impact of trabectedin on seven chosen domains being primarily global QoL, with role functioning, physical functioning, cognitive functioning, fatigue, diarrhea, and nausea and vomiting as secondary key issues, both during and after treatment. A secondary objective is to evaluate the effect of the treatment on the remaining symptoms and functioning scales as treatment-related side effects may have a (temporary) negative influence on the health related domains of HRQoL of these patients. HRQoL will be measured using the QLQ-C30 (v3) and the BN-20 module.

1 Background and introduction

1.1 Meningioma

Meningiomas account for about 24-30% of primary intracranial tumors and occur at an annual incidence rate of up to 13 per 100 000. Most meningiomas are benign (WHO grade I) and curable by resection. However, up to 20% of meningiomas show aggressive behavior with tumor recurrences and infiltration of the surrounding tissues (bone, brain, or soft tissue). WHO grade II (chordoid, clear cell, atypical) and WHO grade III (papillary, rhabdoid, anaplastic/malignant) meningiomas are characterized histopathologically by increased numbers of mitotic features, and have increased risk for unfavorable clinical course.

Owing to the rarity of aggressive meningiomas, there is lack of evidence from systematic studies to guide treatment. Until now, maximal resection and postoperative radiotherapy have emerged as the most commonly used therapy for WHO grade II and III meningiomas. For recurrent disease, there are few therapy options. Repeated surgery or radiotherapy may achieve local tumor control in some patients. Medical therapy of recurrent high-grade meningioma is challenging, as no standards are defined. Recently, the RANO group has summarized and reviewed outcome data for surgery- and radiotherapy-refractory WHO II and III meningiomas (Ref. 1). Disease stabilization was reported for a number of agents including hydroxyurea, CAV chemotherapy (cyclophosphamide, doxorubicin, and vincristine), interferon-alpha, octreotide, Sandostatin LAR, erlotinib, vatalinib, sunitinib and bevacizumab (Ref. 1). However, these data come only from small case series and no randomized studies are available. Reported median progression-free survival times and overall survival times for recurrent WHO grade II and III tumors range from 9 to 30.4 weeks and from 7 to 13 months, respectively. Novel therapies for this indication are urgently needed.

1.2 Trabectedin

The anticancer compound trabectedin (ET743, trade name: Yondelis) (Ref. 2) is a tetrahydroisoquinoline molecule originally isolated from the sea squirt Ecteinascidia turbinate (Ref. 3). The mode of action of trabectedin is not completely understood. However, it is known that the drug binds to the minor groove of the deoxyribonucleic acid (DNA) double helix forming trabectedin-DNA adducts that bend the DNA towards the major groove. Furthermore, trabectedin might affect diverse DNA binding proteins including several transcription factors and DNA repair mechanisms. The alterations induced by the drug activate the nucleotide excision repair (NER) pathway, which is required for maximum activity of trabectedin, while its activity is retained in mismatch repair-deficient cells. In vitro studies elucidated that trabectedin selectively inhibits the transcription of several genes, particularly those encoding the multidrug resistance protein 1, heat shock protein 70, and the cyclin-dependent kinase inhibitor p21WAF1/Cip1 contributing to the induction of programmed cell death. In addition, trabectedin has been shown to deplete tumor-associated macrophages and act as an anti-angiogenic agent (Ref. 3, Ref. 4, Ref. 5, Ref. 6).

Trabectedin has been shown to be active against a wide variety of cell lines and xenografts derived from several solid tumor types. In early clinical trials, trabectedin was active against several solid tumors including breast cancer, prostate cancer, renal cancer, melanoma, and non-small cell lung cancer.

As of 1 July 2013, approximately 9,015 subjects with advanced malignancies have been treated with trabectedin, administered either as a single agent or in combination with other chemotherapeutic agents (Ref. 2). Trabectedin is generally well tolerated with manageable and mostly reversible adverse effects like transaminase elevations, myelosuppression, nausea, emesis, and fatigue. Creatine phosphokinase/kinase elevations (based on laboratory values) and rhabdomyolysis are also observed.

Trabectedin is an emetogenic drug and prophylactic anti-emetic treatment is recommended.

Trabectedin has been approved and is routinely used in patients with advanced soft-tissue sarcoma (STS) who have failed or are not eligible for first line therapy with anthracyclines and ifosfamide and in patients with platinum-sensitive recurrent ovarian cancer in combination with pegylated liposomal doxorubicin.

According to the approved dosing regimen as single agent, trabectedin is delivered as a 24-hour infusion every 3 weeks (day 1 of each 21-day cycle) at a starting dose of 1.5 mg/m^2.

Several ongoing clinical trials evaluate the activity of trabectedin in additional cancer types, including mesothelioma, pancreatic cancer, uterine leiomyosarcoma, metastatic liposarcoma or leiomyosarcoma. Trabectedin is also further investigated in BRCA1 and BRCA2 mutation carrier and BRCAness phenotype advanced ovarian cancer.

1.3 Study rationale

In a recent study, strong in vitro activity of trabectedin against grade II and grade III meningioma cell lines with induction of distinct cell cycle arrest, down-regulation of multiple cyclins, deregulated expression of cell-death regulatory genes and massive apoptosis has been demonstrated (Ref. 7). In addition, high-grade meningiomas typically show prominent infiltration with tumor-associated macrophages and angiogenesis, which have been shown to be therapeutic targets of trabectedin (Ref. 6). Indeed, favorable disease stabilization has been documented in patient with heavily pretreated malignant meningioma (Ref. 7). These findings provide a rationale for further studying the potential efficacy of trabectedin in high-grade meningioma (Ref. 8, Ref. 9).

Therefore, we decided to conduct a prospective clinical trial evaluating trabectedin in recurrent-high grade meningioma. Due to the lack of reliable historical outcome data and the lack of knowledge on the natural course of these tumors, a randomized trial is necessary to generate informative results. The lack of evidence-based treatment recommendations and the high variability in clinical practice among different centers prevents definition of a standard reference therapy. Therefore, “local standard of care” was chosen as control treatment for the current trial. The statistical design of the current trial follows the recent recommendations provided by the RANO group, which has summarized and reviewed outcome data for surgery- and radiotherapy- refractory WHO II and III meningiomas (Ref. 1). Nevertheless, as no randomized clinical trial data were published and patient outcome is not precisely known in this population, a randomized design comparing the whole PFS distribution was selected. Sample size was computed based on PFS-6 according to reference values provided by the RANO report i.e. a PFS-6 of 15% was considered a realistic outcome estimate in the control arm and a PFS-6 rate of >35% was defined as indicating interesting activity. Secondary end-points include the radiological benefit rate (CR and PR and SD), the overall survival rates at 6 and 12 months, median PFS and OS, tolerability and quality of life.

2 Objectives of the trial

2.1 General objectives

The objective of the study is to investigate whether trabectedin demonstrates sufficient antitumor activity against recurrent grade II or III to justify further investigation in phase III or as adjuvant therapy for newly diagnosed disease after resection and radiotherapy.

2.2 End-points

Primary end-point:

- Progression Free Survival (PFS)

Secondary end-points:

- Progression Free Survival at 6 months (PFS-6), median PFS (mPFS)
- Best overall response (BOR). Objective response (CR/PR), rate and median duration. Complete response (CR), rate and median duration.
- Overall survival (OS), OS probability at 6 (OS6) and 12 months (OS12), median OS (mOS)
- Safety (CTCAE v.4.0)
- Health-related Quality of life (Qol)

3 Patient selection criteria

- Age 18 or older
- Histological diagnosis of WHO grade II (chordoid meningioma, clear cell meningioma, atypical meningioma) or WHO grade III (papillary meningioma, rhabdoid meningioma, anaplastic/malignant meningioma) according to WHO 2007 classification.
- Radiologically documented progression of any existing tumor (growth > 25% in the last year) or appearance of new lesions (including intra- and extracranial manifestations)
- No more option for local therapy (resection or radiotherapy) after maximal feasible surgery and radiotherapy
- No prior systemic anti-neoplastic therapy for meningioma (patient may have received prior radionuclide therapy)
- Measurable disease (10 x10 mm) on cranial MRI no more than 2 weeks prior to randomization.
- WHO performance status 0-2
- Adequate liver, renal and hematological function within 4 weeks prior to randomization, defined as:
  - Neutrophils $\geq 1.5 \times 10^9$/L, hemoglobin ≥ 9 g/dL or hemoglobin ≥ 5.6 mmol/L, platelets $\geq 100 \times 10^9$/L
  - Total Bilirubin ≤ 1 x ULN, SGPT/ALT and SGOT/AST ≤ 2.5 x ULN
  - Alkaline phosphatase ≤ 2.5 x ULN; if alkaline phosphatase > 2.5 ULN, ALP hepatic isoenzyme and/or 5-nucleotidase and/or gamma glutyamyltransferase (GGT) must be within the normal range
  - Albumin ≥ 30 g/L
  - Serum creatinine ≤ 1.5 x ULN
  - Creatinine clearance > 30 ml/min as calculated by Cockcroft and Gault formula (see Appendix E)
  - Creatine phosphokinase (CPK) ≤ 2.5 x ULN
- Normal cardiac function (LVEF assessed by MUGA or ECHO within normal range of the institution), normal 12 lead ECG (without clinically significant abnormalities). The following unstable cardiac conditions are not allowed:
  - Congestive heart failure

- Angina pectoris
- Myocardial infarction within 1 year before registration/randomization
- Uncontrolled arterial hypertension defined as blood pressure ≥ 150/100 mm Hg despite optimal medical therapy
- Arrhythmias clinically significant

- Life expectancy of at least 9 weeks
- No history of any other invasive malignancy within the last 5 years (except adequately treated non-melanoma skin cancer, clinicaly localized and very low risk prostate cancer, and adequately treated cervical intraepithelial neoplasia)
- No serious illness or medical conditions, specifically: active infectious process; chronic active liver disease, including chronic hepatitis B, C or cirrhosis
- No concomitant use of any other investigational agent, phenytoin, or vaccination to yellow fever.
- Women of child bearing potential (WOCBP) must have a negative serum (or urine) pregnancy test within 72 hours prior to randomization (and also within 72 hours prior to the first dose of the study treatment). Women of childbearing / reproductive potential should use adequate birth control measures, as defined below, during the study treatment period and for at least 3 months after the last study treatment. Men who are fertile must use effective contraception during treatment with trabectedin and for 5 months thereafter.
  Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:
  - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
  - progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
  - intrauterine device (IUD)
  - intrauterine hormone-releasing system (IUS)
  - bilateral tubal occlusion
  - vasectomised partner
  - sexual abstinence
- Acceptable birth control methods that result in a failure rate of more than 1% per year include:
  - progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
  - male or female condom with or without spermicide
  - cap, diaphragm or sponge with spermicide

- Female subjects who are breastfeeding should discontinue nursing prior to the first dose of study treatment and until 3 months after the last study treatment.
- No known hypersensitivity or contraindication to trabectedin or any of the ingredients of the trabectedin solution for infusion
- No known MRI or CT, including contrast media, contraindications
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
- Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

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 comparative phase II trial. The Korn design (Ref. 10) will be applied (for detailed statistical considerations see chapter 8).

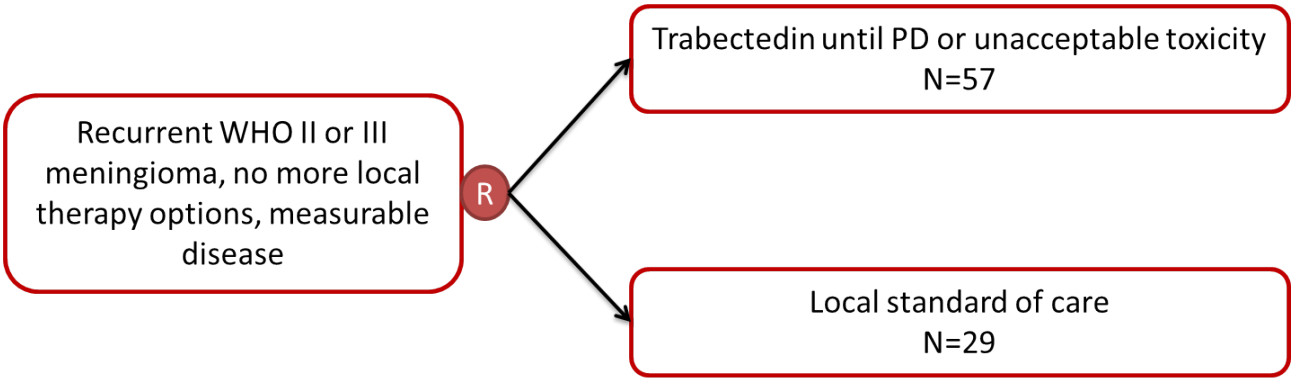
Patients will be randomized at the EORTC headquarters after verification of the eligibility criteria (see chapter 3) to receive one of the following:

- Arm 1 (treatment): Trabectedin delivered as a 24-hour infusion every 3 weeks (day 1 of each 21-day cycle) at a starting dose of 1.5 mg/m^2 body surface area (BSA), until one of the treatment withdrawal criteria has been met.
- Arm 2 (control): Local standard of care.

For the trabectedin arm one cycle will be defined as 3 weeks.

For the control arm one cycle will be defined according to the treatment schedule of the chosen drug.

Disease will be assessed by the Macdonald response criteria (see chapter 7).



5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Therapeutic regimens

5.1.1 Experimental arm

Trabectedin will be given as a 24-hour infusion every 3 weeks at a starting dose of 1.5 mg/m^2 BSA, until one of the treatment withdrawal criteria has been met. Subjects receiving trabectedin are required to receive dexamethasone pretreatment at 20 mg IV, 30 minutes before starting trabectedin.

5.1.2 Control arm

Treatment in the control arm is left to the discretion of the investigator, according to local standard practice, or as referred to by your national authority (see Appendix I). Limited information on the treatment administered will be recorded.

In case of treatment interruption for reasons other than disease progression as part of this study, no other treatment is allowed before disease progression.

5.2 Drug information

5.2.1 General information

The current INN name is trabectedin. The product belongs to the class: Tetrahydroisoquinolone alkaloid. The registered trademark name for trabectedin is Yondelis®.

Trabectedin is provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength of 1 mg. For further information about trabectedin, please refer to the Investigator's Brochure of Yondelis®.

5.2.2 Drug supply

Trabectedin (trade name Yondelis®) will be supplied by PharmaMar free of charge and guidelines for drug resupply will be provided in a separate document.

5.2.3 Packaging, dispensing and storage

Packaging and labelling of Trabectedin will be in accordance with Good Manufacturing Practice (GMP).

For instructions regarding drug inventory, handling, reconstitution, dilution, storage, accountability and disposal, please refer to the Guide of Preparation of Yondelis® (provided as a separate document) for trabectedin.

Trabectedin (trade name Yondelis®) will be labeled according to the current regulatory requirements.

5.2.4 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.

5.3 Initial dose and schedule

Trabectedin must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to personnel specialized in the administration of cytotoxic agents.

For this trial, the recommended starting dose is 1.5 mg/m^2 BSA, administered as an IV infusion over 24 hours with a 3-week interval between cycles. Administration through a central venous line is strongly recommended.

All patients must be premedicated with corticosteroids such as dexamethasone 20 mg IV, 30 minutes before each trabectedin infusion; not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

5.4 Treatment duration

Treatment should be administered until one of the withdrawal criteria has been met (see section 5.5). There is no pre-defined limit to the number of cycles to be administered.

5.5 Withdrawal criteria

The treatment will always be discontinued in case of any of the events mentioned below, whichever comes first:

- disease progression
- excessive toxicity precluding further therapy, according to the responsible physician
- patient refusal
- pregnancy
- investigator decision based on the patient's best interest, even without documented progression
- administration of concomitant drugs not allowed by the protocol (see chapter 5.7)
- if entire study is terminated for medical or ethical reasons

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

After progression, the treatment will be left to the discretion of the treating physician. Any anti-cancer therapy other than the study drug given as single agent before disease progression within the protocol will not be considered as part of the protocol treatment and will be considered as protocol violation.

5.6 Dose and schedule modifications

After an adverse event, patients should be under surveillance until the situation has stabilized or completely resolved.

5.6.1 Trabectedin

At each visit during the treatment period, patients should first be evaluated for the occurrence of adverse events and laboratory abnormalities.

Specific recommendations for management of these possible adverse events along with guidelines for dose delay/modification or discontinuation of study treatment are provided below.

5.6.1.1 Dose reductions

Prior to re-treatment, patients must fulfill the eligibility criteria. If any of the following events occur at any time between cycles, the trabectedin dose must be reduced to 1.2 mg/m^2 BSA in subsequent cycles.

- Neutropenia < 0.5 x 10^9/L lasting for more than 5 days or associated with fever or infection.
- Thrombocytopenia < 25 x10^9/L
- Increase of bilirubin > ULN.
- Alkaline phosphatase > 2.5x ULN and GGT > ULN
- Increase of aminotransferases (AST or ALT) > 2.5x ULN which has not recovered to < 2.5x ULN by day 21 not explained otherwise
- Any other Grade 3 or 4 adverse reactions (such as CPK elevation, nausea, vomiting, fatigue).

In order to adequately assess the duration of these events, it is recommended to perform weekly assessments.

Once a dose has been reduced because of toxicity, dose escalation in the subsequent cycles is not allowed. If any of these toxicities reappear in subsequent cycles, the trabectedin dose must be further reduced to 1 mg/ m^2 BSA. In the event that further dose reductions are necessary according to the above criteria, treatment should be discontinued. Colony stimulating factors can be administered for hematologic toxicity (neutropenia or febrile neutropenia) in subsequent cycles according to local standard practice.

5.6.1.2 Re-treatment criteria

- A maximum delay of 3 weeks from the due date for next infusion is allowed for recovery from toxicity in the preceding cycle of treatment.
- The following criteria should be met before the next infusion:

Hematological parameters	**Value at day 1 of new treatment cycle**
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
Platelet count	≥ 100 x 10^9 /L
Neutrophil count	≥ 1.5 x 10^9 /L
Serum chemistry parameters	**Value at day 1 of new treatment cycle**
Creatinine clearance	≥ 30 mL/min
Creatine phosphokinase	≤ 2.5 x ULN
Total bilirubin	≤ ULN
ALT or AST	≤ 2.5 x ULN
Alkaline phosphatase	≤ 2.5 x ULN
Albumin	≥ 25 g/L
Non hematological – non serum chemistry parameters	**Status at day 1 of new treatment cycle**
Severity of other adverse event has to recover to ≤ Grade 1	

5.6.1.3 Treatment discontinuation

In the event that more than two dose reductions are required or a delay of more than 3 weeks from the due date for next infusion are necessary, patient must go off protocol treatment.

5.6.1.4 Nausea and vomiting

Grade 3 or 4 vomiting and nausea are commonly reported during trabectedin treatment. All patients must be premedicated with corticosteroids such as dexamethasone. Additional anti-emetics may be administered as needed.

5.6.1.5 Injection site reactions

The use of central venous access is strongly recommended. Patients may develop a potentially severe injection site reaction when trabectedin is administered through a peripheral venous line.

There have been few reported cases of trabectedin extravasation, with subsequent tissue necrosis requiring debridement. There is no specific antidote for extravasation of trabectedin. Extravasation should be managed by local standard practice.

5.6.1.6 Rhabdomyolysis and severe CPK elevations

Trabectedin must not be used in patients with CPK > 2.5x ULN. Rhabdomyolysis has been uncommonly reported, and severe CPK elevations were observed in 4.3% of patients treated with trabectedin monotherapy, usually in association with myelotoxicity, severe liver function test abnormalities or renal failure. Therefore, CPK should be closely monitored whenever a patient may be experiencing any of these toxicities or muscle weakness or muscle pain. If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated. Treatment with trabectedin should be discontinued until the patient fully recovers.

Caution should be taken if medicinal products associated with rhabdomyolysis (eg, statins) are administered concomitantly with trabectedin, since it is unknown whether the risk of rhabdomyolysis may be increased in these patients.

5.7 Concomitant treatments

All patients must receive 20 mg of dexamethasone or an equivalent 30 minutes before administration of trabectedin not only as anti-emetic prophylaxis, but also because it appears to provide hepatoprotective effects. Additional anti-emetics may be administered as needed.

5.7.1 Potential Impact of other medications on trabectedin and other concomitant therapies

- Results from the population pharmacokinetic analyses (n = 831 subjects) indicated that the plasma clearance of trabectedin was 19% higher in subjects who received any concomitant dexamethasone administration relative to those who did not.
- Since trabectedin is metabolized mainly by CYP3A4, the concentrations of trabectedin in plasma are likely to be increased or decreased in patients who are co-administered drugs that potently inhibit (eg, oral ketoconazole, fluconazole, ritonavir, clarithromycin, or aprepitant) or induce (eg, rifampin, phenobarbital, Saint John's Wort), respectively, the activity of this isoenzyme. The use of potent CYP inhibitors or inducers with trabectedin should be avoided, if possible. If concomitant use of a CYP3A4 inhibitor is required, patients should be closely observed for toxicities, and dose delays and reductions should occur as per the treatment guidelines described in this protocol
- Caution should be taken if medicinal products associated with hepatotoxicity are administered concomitantly with trabectedin, since the risk of hepatotoxicity may be increased.
- Concomitant use of trabectedin with phenytoin may reduce phenytoin absorption leading to an exacerbation of convulsions. Combination of trabectedin with phenytoin or live attenuated vaccines is not recommended and with yellow fever vaccine is specifically contraindicated
- Alcohol consumption must be avoided during treatment with trabectedin due to the hepatotoxicity of the medicinal product
- Preclinical data have demonstrated that trabectedin is a substrate to P-gp. Concomitant administration of inhibitors of P-gp, e.g. cyclosporine and verapamil, may alter trabectedin distribution and/or elimination. The relevance of this interaction e.g. central nervous system toxicity has not been established. Caution should be taken in such situations.
- Caution should be taken if medicinal products associated with rhabdomyolysis (e.g. statins), are administered concomitantly with trabectedin, since the risk of rhabdomyolysis may be increased.

5.7.1.1 Concomitant anti-cancer therapy

- No concomitant anti-cancer therapy including systemic therapy, radiotherapy, or surgery while on protocol treatment is allowed.
- No concomitant other investigational agent while on protocol treatment is allowed.

5.7.1.2 Permitted medications

- The use of growth factors is permitted

6 Clinical evaluation, laboratory tests and follow-up

The schedule of evaluation as described below applies to both treatment arms. A treatment cycle is defined as 3 weeks in the experimental arm and 3 or 4 weeks in the control arm, whatever is more appropriate for the selected treatment. Disease evaluation (MRI and/or CT) should follow exactly the schedule described below, irrespective of the treatment arm.

Treatment should start within an acceptable delay from randomization. A maximum delay of 21 days is accepted.

6.1 Within 4 weeks prior to randomization and within 4 weeks prior to treatment start

All evaluations performed more than 28 days prior to treatment start must be repeated.

- Informed consent
- Medical history and demographics (age, gender, medical conditions at entry)
- Clinical examination (including WHO performance status, neurological examination, blood pressure, pulse rate, body weight, height and body temperature)
- Recording of corticosteroid dose
- Assessment of all adverse events
- Cardiac monitoring: 12-lead ECG, LVEF (MUGA or echo)
- Complete blood counts will be performed, to include hemoglobin, white blood cells, neutrophils, lymphocytes, platelets.
- A serum chemistry assessment to include at least creatinine, total bilirubin, ALT, AST, alkaline phosphatase (ALP), CPK, albumin, LDH, sodium, potassium, glucose, calcium, hepatic isoenzymes 5-nucleotidase (if applicable), GGT (if applicable).
  - Alkaline phosphatase ≤ 2.5 x ULN; if alkaline phosphatase > 2.5 ULN, ALP hepatic isoenzyme and/or 5-nucleotidase and/or gamma glutyamyltransferase (GGT) must be within the normal range. Creatinine clearance will be calculated by Cockcroft and Gault formula (see Appendix E)
  - For the serum chemistry parameters not collected on the Serum Chemistry form: in case of abnormal value please record it as adverse event on the Adverse Event forms (grade, relationship, seriousness).
- A serum pregnancy test is required in women of reproductive potential within 72 hours prior to randomization (and also within 72 hours prior to treatment start). The pregnancy test is to be repeated during protocol treatment every two treatment cycles.
- HRQoL: QLQ-C30 (v3) and the BN-20 questionnaire (for more information see chapter 10).

6.2 Within 2 weeks prior to randomization and within 4 weeks prior to treatment start

Baseline tumor evaluations performed more than 28 days prior to treatment start must be repeated.

- Tumor evaluation (no more than 2 weeks prior to randomization): assessed by standard methodology using cranial MRI. CT thorax/abdomen should be performed if clinically indicated. The same method should be used for repeated measurements throughout the study.

6.3 During treatment

The following need to be performed on day 1 of each treatment cycle or within 72 hours before:

- Clinical examination (WHO PS, blood pressure, pulse rate, body weight, and body temperature).
- Assessment of all adverse events that have occurred since the previous visit and ongoing events from previous cycles should be followed.
- Complete blood counts to include hemoglobin, white blood cells, neutrophils, lymphocytes, platelets. For the experimental arm only, additional monitoring of hematological values should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles
- A serum chemistry assessment to include at least creatinine, total bilirubin, ALT, AST, ALP, CPK, albumin, LDH, sodium, potassium, glucose, calcium. For the experimental arm only, additional monitoring of serum chemistry values should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles
  - If ALP > 2.5 ULN, ALP hepatic isoenzyme 5-nucleotidase and/or GGT tests must be performed; ALP hepatic isoenzyme or 5-nucleotidase and/or GGT must be within the normal range.
  - Creatinine clearance will be calculated by Cockcroft and Gault formula (see Appendix E)
  - For the serum chemistry parameters not collected on the Serum Chemistry form: in case of abnormal value please record it as adverse event on the Adverse Event forms (grade, relationship, seriousness).
- Cranial MRI every 9 weeks from randomization and if clinically indicated
- Recording of corticosteroid dose every 9 weeks
- CT thorax/abdomen only if clinically indicated; if tumorous or unclear lesions detected repeat CT every 9 weeks and if clinically indicated
- HRQoL: QLQ-C30 (v3) and the BN-20 questionnaire: regardless the treatment arm, at week 3, week 6 and week 12 after treatment start (for more information see chapter 10).
- Pregnancy test (every two cycles)

6.3.1 Disease evaluation

- The disease will be assessed every 9 weeks by cranial MRI, regardless of interruptions and delays in therapy.
  - All organs that were found to be involved at the initial assessment will be re-investigated by the same method.
  - All lesions chosen as target during the initial assessment will be measured by the same method and, if possible, by the same person;
  - All investigations will be consistent with baseline in order that the development of new lesions in previously normal areas can also be determined.

6.4 After the end of treatment (Follow-up)

6.4.1 30 days after last administration of study drug

- Clinical examination (WHO performance status, blood pressure, pulse rate, body weight and body temperature)
- All ongoing adverse events from previous cycles should be followed until their resolution or stabilization or until the start of new anticancer therapy.
- Pregnancy test
- Complete blood counts to include hemoglobin, white blood cells, neutrophils, lymphocytes, platelets.
- A serum chemistry assessment to include at least creatinine, total bilirubin, ALT, AST, ALP, GGT, CPK, albumin, LDH, sodium, potassium, glucose, calcium.
  - If alkaline phosphatase > 2.5 ULN, hepatic isoenzymes 5-nucleotidase or GGT determinations must be performed; hepatic isoenzymes 5-nucleotidase and/or GGT must be within the normal range.
  - Creatinine clearance will be calculated by Cockcroft and Gault formula (see Appendix E)
  - Only the following parameters will be collected on the serum biochemistry form: creatinine, total bilirubin, ALT, AST, ALP hepatic isoenzymes 5-nucleotidase (if applicable), GGT (if applicable), CPK.
  - For the serum chemistry parameters not collected on the Serum Chemistry form: in case of abnormal value please record it as adverse event on the Adverse Event forms (grade, relationship, seriousness.

6.4.2 3 months after last administration of study drug

- Pregnancy test

6.4.3 Until PD or start of new anticancer therapy

- Cranial MRI every 9 weeks and if clinically indicated
- Recording of corticosteroid dose every 9 weeks
- CT thorax/abdomen only if clinically indicated; if tumorous or unclear lesions detected repeat CT every 9 weeks or if clinically indicated
- Clinical examination (WHO PS only) every 9 weeks and as clinically indicated
- All ongoing adverse events should be followed every 9 weeks until resolution or stabilization.

HRQoL: QLQ-C30 (v3) and the BN-20 questionnaire at month 6 after treatment start for all patients regardless of treatment arm or progression status (see chapter 10).

Patient should be followed for survival every 9 weeks until PD or one year after randomization (whatever happens first) and every 12 weeks thereafter.

6.5 Summary table

	Within 4 weeks prior to randomization[7]	Within 2 weeks prior to randomization	During treatment		After treatment		
			On day 1 of each cycle or within 72 hours before	Every 9 weeks	End of treatment (30 days after last treatment administration)	Until PD every 9 weeks	After PD, every 9 weeks for the first year from randomization and every 12 weeks thereafter
Informed consent	♦						
Clinical examination	♦		♦		♦	♦[8]	
Medical history, demographics	♦						
Recording of corticosteroid dose	♦			♦		♦	
Adverse events assessment	♦		♦		♦	♦	
ECG	♦						
LVEF	♦						
Hematology [3]	♦		♦		♦		
Serum chemistry [4]	♦		♦		♦		
Pregnancy test	♦ [1]		♦ [1]		♦ [2]		
Quality of life questionnaire (QLQ-C30 and BN20)	♦		♦[5]				
Tumor evaluation using cranial MRI		♦[10]		♦		♦[9]	
CT torax/abdomen		♣		♣[6]		♣[6]	
Survival						♦	♦

♦ mandatory ♣ if clinically relevant

1. Perform only in women of childbearing potential. The pregnancy test has to be done within 72h prior to randomization and also within 72 hours prior to treatment start and repeated during protocol treatment every two treatment cycles.
2. Pregnancy test must be repeated at 30 days and 3 months after last treatment dose.
3. Hematology test includes white blood cells, neutrophils, lymphocytes, platelets, hemoglobin counts. Note for the experimental arm only: additional monitoring of hematological values should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles.
4. Serum chemistry includes at least creatinine, total bilirubin, ALT, AST, ALP, CPK, albumin, LDH,

sodium, potassium, glucose, calcium. If alkaline phosphatase > 2.5 ULN, ALP hepatic isoenzyme and/or 5-nucleotidase and/or gamma glutyamyltransferase (GGT) must be performed. Note: for the experimental arm only, additional monitoring of biochemical parameters (ALP, total bilirubin, CPK, and aminotransferases [AST and ALT]) should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles.
5. QLQ-C30 (v3) and BN-20: at end of week 3/end of cycle 1, end of week 6/end of cycle 2, end of week 12/end of cycle 4 after treatment start, and at month 6 after treatment start regardless of treatment arm or progression status.
6. Only in patients with known tumorous or unclear lesions on prior CT
7. All evaluations performed more than 28 days prior to treatment start must be repeated
8. Only WHO PS
9. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 9 weeks for the first year from randomization and every 12 weeks thereafter.
10. MRI scans acquired up to 2 years before inclusion of patients into this trial should also be submitted.

7 Criteria of evaluation

7.1 Evaluation of efficacy

Objective tumor response and time to progression will be measured according to the Macdonald response criteria (Ref. 11).

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

The following paragraphs are a quick reference to the Macdonald response criteria.

7.1.1 Measurability of tumor lesions at baseline

7.1.1.1 General method of response assessment

Objective response to treatment is based on assessment at the treating site, following the provided imaging guidelines.

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 for this protocol is based on neuro-radiological imaging (MRI).

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. The initial comparison must be done against the baseline scan. 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, i.e. the scan showing the maximum response (= minimum tumor size) during or after treatment. In assessing response, changes on T1-Gd+ images must be taken into consideration.

7.1.1.2 Definition

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with MRI scan. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component and leptomeningeal disease are non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.

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".

- By definition, non-target lesions are those that do not meet the criteria for target lesion. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

7.1.2 Tumor response evaluation

All patients will have their overall response (OR) from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted. Clinical evaluation must be stable or improving. No steroids should be needed.

Partial Response (PR): at least a 50% decrease in the sum of the product of perpendicular diameters of the target lesions, as compared to baseline. Non target lesions must be non-PD. Clinical evaluation must be stable or improving. Steroid dose must be stable or diminishing.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest tumor measurement recorded during the study. Clinical evaluation must be stable or improving. Steroid dose must be stable or diminishing.

Progressive Disease (PD): at least a 25% increase in the sum of products of perpendicular diameters of the measured lesions taking as references the smallest tumor measurement recorded during the study (including the baseline scan). Appearance of new lesions (including extracranial) will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, 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, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used. Worsening of the clinical evaluation should also be recorded as PD.

Table 1: Macdonald response criteria

	CR	PR	SD	PD
T1-Gd+	0	decrease ≥ 50%	decrease < 50% or increase < 25%	increase ≥ 25%
New Lesion	no	No	no	Yes*
Steroids	no	stable or decreasing	stable or decreasing	NA
Clinical evaluation	stable or improving	stable or improving	stable or improving	worsening
	All	All	All	Any

* including extracranial lesions

7.1.2.1 Frequency of tumor re-evaluation

Cranial MRI every 9 weeks from randomization until progression.

CT thorax/abdomen only if clinically indicated; if tumorous or unclear lesions detected repeat CT every 9 weeks and as clinically indicated.

In the present study, tumors will be re-evaluated every 9 weeks during treatment. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 9 weeks for the first year from randomization and every 12 weeks thereafter.

7.1.2.2 Date of progression

This is defined as the first day when the Macdonald response criteria for PD are met.

7.1.3 Progression Free Survival

Progression Free Survival (PFS) will be measured from the date of randomization until the date of first objective progression or the date of patient's death whichever occurs first. Patients without evidence of progression will be censored at the last follow-up visit date. If a patient received a second anti-tumoral therapy without prior documentation of disease progression, the patient will be censored at the date of starting new anti-tumoral therapy.

7.1.4 Overall Survival

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, survival will be censored at last follow-up visit date.

7.1.5 Overall response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable. Early death is defined as any death occurring before the first per protocol time point of tumor re-evaluation.

Patients' response will be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria.

7.1.6 Best overall response

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

7.1.7 Response duration

Objective response duration (CR/PR) and complete response (CR) will be measured similarly to PFS (see above) but starting from the time measurement criteria for CR/PR or CR (whichever is first recorded) are first met.

7.2 Evaluation of safety

7.2.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

Only the worst grade per CTCAE category will be recorded per cycle. The collection period will start from randomization up to 30 days after administration of the last dose of protocol treatment or until the start of a new antitumor therapy, whichever occurs first.

All adverse events must be followed until resolution or stabilization.

Whenever possible, the Investigator will record the main diagnosis instead of the signs and symptoms normally included in the diagnoses.

Investigators must pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification.

7.2.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page www.eortc.org\investigators-area\ctc.

The highest CTCAE grading per cycle and per patient will be computed at the EORTC HQ for analysis.

Planned safety analysis and tabulations are described in the statistics section.

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 on Reporting Serious Adverse Events)

7.2.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events at least with reasonable possibility related to study treatment). The cause of death must be reported as "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).

7.2.5 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

This trial is a phase II with a Korn superiority design comparing PFS between trabectedin and control with a treatment allocation ratio equal to 2:1 at randomization. Based on RANO recommendation (Ref. 1), PFS-6=15% was assumed in the control arm and 35% in the trabectedin arm (i.e. 20% difference). Assuming PFS follows an exponential distribution, this corresponds to a treatment Hazard Ratio (HR) equal to 0.55. Based on the logrank test, a type I error equal to 10% one-sided (20% two sided), a power equal to 85%, 72 progressions or deaths are needed to assess the targeted effect. 86 eligible patients who started their treatment (per protocol population) should be recruited (57 trabectedin, 29 control). Assuming 7.17 patients per month (1.99 months 0-4, 3.55 months 4-8, 5.29 months 8-12 and 7.17 beyond 12 months), about 18 months of recruitment are needed. Events should be observed shortly (about 3-4 months) after end of accrual.

8.1.2 Randomization and stratifications

All patients entered will be centrally randomized at the EORTC Headquarters (for practical details, see chapter on randomization procedure). The minimization technique (Ref. 12) 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 (Ref. 13). 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. Stratification factors are: institution, pathological grade (II, III), age (≤, > 60) and performance status (0, >0).

8.2 Statistical analysis plan

8.2.1 Primary and secondary endpoints

8.2.2 Analysis populations

- Intention-to-treat population: all randomized patients will be analyzed in the arm they were allocated by randomization
- Per protocol population: all patients who are eligible and have started their allocated treatment (at least one dose of Trabectedin or start of local standard of care therapy)
- Safety population: all patients who have started their allocated treatment (at least one dose of Trabectedin or start of local standard of care therapy)

A patient will be considered to be eligible if the patient did not have any deviation from the patient selection criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician during medical review.

8.2.3 Statistical methods

8.2.3.1 Progression Free Survival

In the per protocol population:

PFS will be compared between trabectedin and control arm when 71 PFS events are observed. A Cox regression model including treatment and stratification factors at randomization (except institution) will be fit. If for a factor, Proportional Hazards assumptions (PH) are not respected (assessed by Schoenfeld residuals), the model will be stratified (i.e. not adjusted) by this factor. The superiority of trabectedin against the control arm will be tested at 10 % one-sided (20% two-sided) significance level. The treatment HR estimate will be presented with 90 % one-sided confidence interval (CI). 95% CI will also be presented. The PFS probability at 6 months (PFS-6) and the median PFS (mPFS) will be extracted from the Kaplan-Meyer PFS curve. 95% confidence intervals will be computed based on the Greenwood's formula. For the median the Reflected Method will provide 95% confidence intervals.

8.2.3.2 Radiological response

In the per protocol population:

The best overall response will be presented in contingency table with numbers and percentages. The objective response (CR/PR) and complete response rates will be reported with exact (binomial) 95% confidence interval. The medians of objective (PR/CR) and complete (CR) response duration will be extracted from their respective Kaplan-Meier curves. The Reflected Method will provide 95% confidence interval.

8.2.3.3 Overall Survival

In the per protocol population:

OS will be compared between trabectedin and control arm. A Cox regression model including treatment and stratification factors at randomization (except institution) will be fit. If for a factor, Proportional Hazards assumptions (PH) are not respected (assessed by Schoenfeld residuals), the model will be stratified (i.e. not adjusted) by this factor. The superiority of trabectedin against the control arm will be tested at 5% two-sided significance level. The treatment HR estimate will be presented with 95% CI. The OS probability at 6 months (OS6), at 1 year (OS12) and the median OS (mOS) will be extracted from the Kaplan-Meyer OS curve. 95% confidence intervals will be computed based on the Greenwood's formula. For the median the Reflected Method will provide 95% confidence intervals.

8.2.3.4 Safety and tolerability

In the safety population at baseline and during treatment and follow-up:

The safety and tolerability analyses will be presented at baseline and for the whole study duration. Severe grades which did not resolve after treatment discontinuation or emerged during follow-up will be identified and listed. All forms up to the last safety assessment before progression or start of further antitumoral therapy will be used. 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 accounted for in whole study duration safety analyses. Laboratory and AE events occurring in patients who did not start their allocated treatment will be reported separately.

8.2.3.4.1 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.

8.2.3.4.2 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.

8.2.3.4.3 All AEs

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

8.2.3.4.4 SAEs

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

8.2.3.4.5 Related AEs

The worst grade of each related AE item will be identified for each patient. Frequencies and percentages of each CTCAE term will be tabulated grouped by SOC. Tables with all grades and grade 3/4 frequencies and percentages will be provided.

8.2.4 Pre-planned sensitivity or exploratory analyses

There is no pre-planned sensitivity analysis. Exploratory analyses may be performed on the basis of subgroup of patients (e.g. Ki67 expression, microvascular density, and density of tumor-associated macrophages), but results of these exploratory analyses may not serve as a basis for drawing conclusions concerning protocol treatment efficacy, and the reasons for excluding patients should be clearly reported.

Below a power table. It assumes worse prognosis in a high proliferation subgroup. Different rates of high proliferation and prognostic detrimental effect (HR>1) are computed.

Power to show the prognostic effect of a proliferation index in the whole population with 71 PFS events at 2.5% significance (one-sided).

	Hazard Ratio			
High proliferation rate	HR=1.95	HR=2	HR=2.5	HR=3.05
10%	<80%	41.5%	63.5%	80%
20%	<80%	64.5%	87%	>80%
30%	<80%	76%	94%	>80%
40%	<80%	81.5%	96.5%	>80%
50%	80%	83%	97%	>80%

8.2.5 Prognostic factor analyses

Data of this trial will be included in the EORTC Brain Tumor data warehouse for further pooled data analyses of prognostic factors, prognostic models development and subgroup analyses.

8.2.6 Data re-coding 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) and Mean (Standard Deviation).

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

8.3 Interim analyses

A futility interim analysis based on boundaries from Rho family (rho=1.625) is planned when half of events (36) are observed. This should occur about 14.5 months after start of accrual when 61 patients are recruited. In absence of effect i.e. an observed PFS HR>=1, trial would be stopped for futility. With this boundary, there is 50% chance to stop the trial for lack of effect if the null hypothesis is true (H0). Safety will be reviewed by the EORTC DSMB every 6 months and by the EORTC IDMC at the time of futility analysis together with efficacy data.

8.4 End of study

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

1. Thirty days after last treatment administration to the last patient on protocol

2. The trial is mature for the analysis of the primary endpoint as defined in the protocol

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

Follow up data might be captured for all patients after the end of study declaration in order to document secondary endpoints with more precision i.e. overall survival, outcome of patients according to molecular and pathological subgroups (see chapter 8 and 11).

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

Relatively little is known about the health-related quality of life (HRQoL) of meningioma patients. This is remarkable considering the growing interest in incorporating HRQoL as secondary outcome measure in primary brain tumor clinical trials (Ref. 14). Data that do exist mainly concern WHO grade I meningioma patients. Patients with suspected WHO grade I meningioma already have limitations in cognitive functioning and HRQoL (Ref. 15), while HRQoL slightly improved after surgery in a mixed group of WHO I-III patients (Ref. 16). Van Nieuwenhuizen et al did not demonstrate any differences in HRQoL between WHO I meningioma patients who had undergone surgery with or without postoperative irradiation on the one hand, and age-, gender-, and education-matched healthy controls on the other hand (Ref. 17). Another study confirmed that HRQoL long-term outcome of the majority of WHO grade I meningioma patients is comparable to that of the general population, except for role limitation caused by physical functioning. However, patients with cognitive deficits and those using anti-epileptic drugs (AEDs) had a compromised HRQoL (Ref. 18). Altogether, currently the scarce available data suggest that HRQoL might initially be compromised in meningioma patients, but is comparable to healthy controls when adequate treatment has been installed, apart from a subgroup of patients with severe cognitive deficits or on AED. Unfortunately, no specific data on HRQoL of WHO grade II and III patients are available.

Evaluation of HRQoL is important to get a better understanding of the balance between the effects of treatment response and treatment-related side-effects from the perspective of the patients. The role of chemotherapy in WHO II and III meningioma is far from being established. The major endpoint in the current randomized phase II trial is to compare PFS between the experimental (trabectedin) and the control arm (local standard of care) for patients with a poor prognosis. Trabectedin has been shown to be well tolerated with manageable and mostly reversible adverse effects such as transaminase elevations, myelosuppression, nausea, vomiting and fatigue. Only few patients experience severe toxicities like skin and soft tissue necrosis due to extravasation or rhabdomyolysis. If treatment-related side effects influence the HRQoL of the patients in a negative way, however, possible advantages in terms of PFS will have to be balanced against the burden of treatment. It is for this reason that HRQoL is included as a secondary endpoint in this study.

10.1 Objective

The study hypothesis is that trabectedin chemotherapy will result in a PFS-6 of 35% compared to 15% in the control arm. In the present study, HRQoL is an important secondary endpoint. The main objective of HRQoL assessment within this trial is to determine the impact of trabectedin on **seven chosen domains being primarily global QoL, with role functioning, physical functioning, cognitive functioning, fatigue, diarrhea, and nausea and vomiting as secondary key issues.** It is expected that these were likely to be most affected in patients undergoing trabectedin chemotherapy. The Ho hypothesis will be tested to show that there is no difference between patients in both arms during and after treatment for the selected scales. A secondary objective is to evaluate the effect of the treatment on the remaining symptoms and functioning scales as treatment-related side effects may have a (temporary) negative influence on the health related domains of HRQoL of these patients.

10.2 HRQoL instrument

Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This instrument is composed of multi-item and single-item scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting and pain), a global health status/QoL 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. 19, Ref. 20, Ref. 21) The average time to complete the questionnaire is approximately 10 minutes. The EORTC QLQ-C30 version 3 has been translated in over 50 languages according to a standardized translation procedure.

The domains of interest as specified in the previous paragraph are covered by the Global QoL/health, role functioning, physical functioning, cognitive functioning, fatigue, diarrhea, and nausea and vomiting scales.

In order to address particularities and special dimensions that pertain to the HRQoL issues in brain tumors, the QLQ Brain Cancer module (QLQ-BN20) will be added to the HRQoL evaluations in this trial. This module has been developed specifically for use in brain tumor patient populations. The QLQ-BN20 has shown its validity and utility. (Ref. 20, Ref. 21) The module consists of 20 items, grouped into 4 domains (future uncertainty, visual disorder, motor dysfunction and communication deficit) and 7 single items (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs and bladder control).

10.3 Study design

Patients are eligible for the quality of life assessment in this study if they fulfill the eligibility criteria (Chapter 3) and, complete the baseline HRQoL questionnaire before randomization. Patients will be informed in the written patient informed consent form that they will have to undergo repeated quality of life assessments while involved in this trial. HRQoL will be a secondary endpoint and evaluated in a longitudinal design in all patients entered in this study. HRQoL is a mandatory requirement.

10.3.1 HRQoL schedule - timing and location

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 G). The pre-treatment questionnaires must be filled within 4 weeks prior to randomization. Subsequent questionnaires are filled in as described in the time schedule in this paragraph.

Electronic copies of the HRQoL questionnaires will be sent to the institutions to be printed. Additional translations can be provided to any institution upon request via the EORTC contact person. The case 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 **prior** to seeing the treating physician at 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.

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

Assessment	Time window
Baseline	Can be completed before or on the day of start of protocol treatment but no earlier than 28 days before.
Week 3 (End of cycle 1)	To be completed during the third week after treatment start while on protocol treatment. If 3 weekly chemotherapy regimen: can be completed during the third week of the first cycle of chemotherapy (D15-D21 of cycle 1).
Week 6 (End of cycle 2)	To be completed during the sixth week after treatment start while on protocol treatment. If 3 weekly chemotherapy regimen: can be completed during the third week of the second cycle of chemotherapy (D15-D21 of cycle 2).
Week 12 (End of cycle 4)	To be completed during the twelfth week after treatment start while on protocol treatment. If 3 weekly chemotherapy regimen: can be completed during the third week of the fourth cycle of chemotherapy (D15-D21 of cycle 4).
At 6 months	Can be completed at any time during the fifth and sixth month after date of randomization regardless of treatment or progression status.

10.3.2 Compliance

Missing data may hamper assessment of HRQoL in clinical trials. This may be because centers do not collect the questionnaires at the appropriate time (unit non-response), and because patients may miss questions within the questionnaires (item non-response). The latter problem occurs less than 2% on average and should not be a problem. The former problem will be minimized by ensuring that participating centers are properly informed and motivated towards HRQoL assessment. During the study, compliance with completing HRQoL questionnaires will be investigated at each time point. The compliance of the HRQoL assessments will also be reviewed twice a year and will be a part of the descriptive report by Data Center for the Group's plenary sessions. The compliance rate between the 2 arms will be compared at each time point using a chi-square test. In order to adjust for the multiplicity of the tests, a Bonferroni adjustment will be made by which each test will be performed at the 0.01 significance level. Should serious volumes of missing questionnaires occur (below 65% at any assessment point) then the protocol writing committee would review the HRQoL assessment in the trial.

Available patient numbers will diminish during the trial due to progression, death, or loss to follow-up. Given the low prognosis of the patient population, the HRQoL assessments appear more frequently early on (first 3 cycles) and only one later follow-up visit is required.

10.4 Statistical considerations

The primary HRQoL endpoint that is considered relevant for this study is **global QOL**. The following scales will be considered as secondary HRQoL endpoints: **role functioning, physical functioning, cognitive functioning, fatigue, diarrhea, and nausea and vomiting**. The other available scales will only be analyzed on an exploratory basis.

A difference of 10 points on the 100-point QLQ-C30 scale between the two arms will be considered as clinically relevant. The standard deviation of this scale is approximately 20 points. With the 1-sided alpha set at 10%, and a target difference of 10 points (effect size of 0.5), a minimum of 89 patients (in a 2:1 randomization) yields 80% power and 76 patients would yield 75% power. Therefore, this study is sufficiently powered to detect differences in HRQoL.

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 summary statistics. The following two summary statistics will be used:

- During treatment: the change from baseline score to the worst score (ie minimum for functioning and global health scale; maximum for symptom scales) reported during treatment per patient will be compared.
- After treatment: the change from baseline score to the score at month 6.

Both summary statistics will be displayed via mean, median and standard deviation per treatment arm. Treatment differences will be displayed via mean differences and corresponding 90% confidence intervals. Treatment comparisons will be done via non-parametric logrank tests for the selected primary and secondary scales. Both statistical and clinical significance will be assessed.

Supportive analyses will be done by calculating the proportion of patients who experience a clinical significant deterioration (i.e. 10 point or more worsening) for both summary statistics.

10.4.1 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 by imputation of plausible values. 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

11.1 HBM-based translational research

Tumor FFPE blocks will be collected in real-time for retrospective central pathology review. In addition, the association of tumor cell proliferation, microvascular density, and density of tumor-associated macrophages with response to treatment will be explored using immunohistochemistry.

Furthermore, the full landscape of potential diagnostic, prognostic, and predictive molecular markers within the tumor samples of the study cohort will be comprehensively profiled along an established pipeline dedicated to meningioma in the Dept. of Neuropathology Heidelberg (Ref. 23, Ref. 24, Ref. 25).

This analytical pipeline includes:

- Next-generation-sequencing (NGS) for a custom panel of 40 genes known to be involved in meningioma development and progression.
- Epigenetic profiling applying the Illumina 850k EPIC array for genome-wide evaluation of CpG-island methylation status. A reference dataset of methylation patterns in meningioma of distinct clinical outcomes has already been generated based on 650 meningioma cases across two independent cohorts. This data serves as basis to allot the novel meningioma samples to epigenetically defined malignancy classes. Based on the array data obtained with this technology, also a high-resolution copy-number profile can be calculated which is of particular interest given the association of chromosomal alterations and progression in meningioma.

All data will be generated and primarily stored at the Dept. of Neuropathology Heidelberg. Within the Dept. of Neuropathology, the data is protected from unauthorized access by the University Hospital Heidelberg firewall system. From there, it will be provided to the EORTC data management for correlation with clinical data including primary and secondary outcomes and imaging data.

All other, not yet-defined translational research performed will be described in appropriate documents and all applicable regulatory and legal requirements will be met.

11.1.1 Biological material required for correlative molecular analysis

To achieve the above mentioned objectives at least one paraffin block from the initial operation (diagnosis) or any operation performed at recurrence will be collected. If a representative FFPE block is not available, the collection of optimally 30, minimally 20 x 5 µm, unstained slides is required (for additional details please also see the HBM guidelines). FFPE tumor material has to be sent to:

Central laboratory

Christian Mawrin
Otto Von Guericke Universitaet Magdeburg - Universitaetsklinik - Department of Neuropathology
Leipziger Str. 44
39120 Magdeburg
Germany (Deutschland)

In order to assess the diagnostic, prognostic, and predictive molecular markers within the tumor samples, the central laboratory will ship FFPE unstained slides to the Dept. of Neuropathology Heidelberg. The leftover material will be stored in the central laboratory in Magdeburg.

Felix Sahm
University of Heidelberg - Institute of Pathology
Department of Neuropathology
Im Neuenheimer Feld 224
D-69120 Heidelberg
Germany

The informed consent for trial participation will explain the need of this material of the initial resection, and eventually subsequent resections for translational research.

11.1.2 Data storage, transfer and development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Bioinformatics and statistical analysis plan will be jointly developed for each project. These documents will be developed and approved before starting any analysis. They will specify the analytical and methodological details. Clinical and patient-reported outcome data will be stored in the EORTC clinical

database and biological investigational data will be stored in respective collaborating institutions. Transfer of data will be performed according to applicable policies in each organization (e.g. EORTC POL008) or according to jointly approved data transfer charters.

11.1.3 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

Biobanking refers to the chain of procedures that encompass the life cycle of the biological material, e.g. from collection, shipping to long term storage and use, and may also be subject to local regulation and/or national/international legislation.

From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects specified in this protocol or defined in the future.

The following principles apply to storage of HBM:

- The collected HBM should be documented, i.e. the amount remaining and its location.

The Study coordinator and the EORTC Brain Tumor Group steering committee will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. In case of absence or inability of the above mentioned steering committee, responsibilities are transferred to the Group and/or EORTC HQ as applicable.

Final decisions on the use of HBM will be determined by a majority vote of the Brain Tumor Group steering committee. Additional expertise may be sought through advisory non-Group steering committee members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

- A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the appropriate Group committee.
- The Group steering committee will prioritize the TR projects. Access procedures defined by the Group steering committee will build on the following key points:
  - Project prioritization
    - should be strongly based on scientific merit,
    - should consider the contribution of the different investigators to the trial and TR project,
    - will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).
  - Protection of confidentiality must be respected.
- An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.

- Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).
- Once Group steering committee prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.
- The EORTC Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the Group steering committee and the TR project leader(s), as needed.

11.2 Imaging-based translational research

Retrospective review of the images will take place for this study. Although treatment decisions are based on objective tumor assessment at the treating sites, retrospective central review will reassess all images to confirm the initial assessment.

Preliminary RANO criteria for response assessment in meningioma were presented in the RANO working group meeting during the 2014 ASCO annual meeting. Publication is expected. In line with the RANO response criteria for high-grade gliomas (Ref. 22), the RANO criteria for response assessment in meningioma take into account two-dimensional tumor measurements on Gd-enhanced MRI, as well as changes in corticosteroid dose and changes in clinical evaluation. In addition, they introduce the concept of minor response (MR), defined as decrease in the sum of lesion diameters between 25% and 50%. The criteria are summarized in table 11.1. The RANO meningioma criteria will be validated in the patients enrolled in the EORTC-1320 trial.

Retrospective studies have indicated that systemic therapy may decrease the growth rate of meningiomas (Ref. 26). MRI scans acquired up to 2 years before inclusion of patients into the EORTC-1320 trial will be collected to investigate whether the growth dynamics of grade II or III meningiomas changes with start of study treatment.

Table 11.1 Summary of preliminary RANO response criteria for meningioma

	CR	PR	MR	SD	PD
T1-Gd+	0	decrease ≥ 50%	decrease < 50% and decrease > 25%	decrease ≤ 25% or increase < 25%	increase ≥ 25%
New Lesion	No	no	no	no	yes
Steroids	No	stable or decreasing	stable or decreasing	stable or decreasing	NA
Clinical evaluation	stable or improving	stable or improving	stable or improving	stable or improving	worsening
	All	All	All	All	Any

For this study, images will be centralized through the EORTC imaging platform. 2D and volumetric measurements will be obtained through retrospective imaging review, aiming to add information towards validation of the RANO response assessment criteria for meningioma.

Tables comparing best overall response to treatment between RANO and MacDonald's Criteria will be presented with frequencies and percentages. Discrepancies will be documented. The difference in PFS (definition above, same for both criteria) will be analyzed by visual comparison of the Kaplan-Meier curves and by tabulating PFS6, PFS9, PFS12 with 95% confidence intervals.

12 Investigator authorization procedure

Investigators will be authorized to 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 in English with a GCP training proof.
- 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.
- The Confirmation of interest by Principal Investigator Form (CIF), 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 CIF.

- Study Agreement between EORTC and investigator's institution.
- 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.

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 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 http://orta.eortc.be/).

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 (http://orta.eortc.be/) and it is updated annually.

Through internet:	http://orta.eortc.be/
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, a unique code to help identify the patient within your institution*)
- patient's birth date (*day/month/year*) or year of birth (as allowed per applicable legislation)

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 SAE form and the Pregnancy notification form which are paper CRFs.

Copies of the Quality of Life should be sent directly to the EORTC Headquarters by one of the following means:

By fax, to the attention of "BTG" Data manager: + 32 2 771 3810

By scanning and e-mailing the forms to 1320@eortc.be (see guidelines for completion of case report forms)

By regular mail to the EORTC Headquarters:

("BTG" Data Manager)

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

SERIOUS ADVERSE EVENTS AND PREGNANCY NOTIFICATION FORMS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter 15 on Reporting Serious Adverse Events).

A. Before the treatment starts:

- The patient must be 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 hour after the randomization on http://rdc.eortc.be/ or on http://www.eortc.org in the investigator area.

The paper CRFs 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).

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 Pregnancy Notification 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.

For trials with paper quality of life forms: a copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. 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.

The EORTC data manager 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.

For trials with paper quality of life forms: if an investigator (or an authorized staff member) needs to modify the paper quality of life form after the copy has been sent to the EORTC Headquarters, he/she should create a request for data correction on a patient level in the VISTA/RDC system.

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.

The following special situations should also be considered AEs, but only when they lead to an adverse reaction:

- Drug overdose;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Off-label use;
- Occupational exposure

- Exposure in uterus.

Any event involving adverse drug reactions, illnesses with onset during the study or exacerbations of pre-existing illnesses should be recorded including but not limited to clinically significant changes in physical examination findings and abnormal objective test findings (e.g., X-Ray, ECG). The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- The test result is associated with clinically significant symptoms, and/or
- The test result leads to a change in the study dosing or discontinuation from the clinical trial, significant additional concomitant drug treatment or other therapy, and/or
- The test result leads to any of the outcomes included in the definition of a SAE, and/or
- The test result is considered to be an AE by the investigator.

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 inpatient hospitalization or prolongation of existing patient hospitalization (unless exempted from SAE reporting (see section 15.2)).
- 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.

A suspected transmission via medicinal product of an infectious agent is also considered a serious adverse reaction.

Death, as such, is the outcome of a SAE and should not be reported as the SAE term itself. Instead the cause of death should be recorded as the SAE term. When available, the autopsy report or its main conclusions in English will be provided to the Sponsor.

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.

Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the Investigator or the treating physician.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

15.2 Exceptions

The following situations shall not 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. However, events requiring hospitalizations or prolongation of hospitalization as a result of a complication of therapy administration or clinical trial procedures will be reported as SAEs.
- Social, technical, administrative and/or convenience admission to a hospital, in absence of a SAE
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure should be reported if meets the definition of an (S)AE. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the (S)AE, and the resulting appendectomy should be recorded as treatment of the 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.
- An emergency visit due to an accident where the patient is treated and discharged.
- When the patient is held 24 hours for observation and finally is not admitted.

- Planned treatments at sites not associated to a hospital and generally considered as minor surgical procedures (i.e., laser eye surgery, arthroscopy, etc).

By EORTC convention, clinical events related to the primary cancer being studied or 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 (i.e. fatal, hospitalization, etc.),.),.), **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

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:

- Trabectedin: most updated Investigator's Brochure.
- Local standard of care treatment: Summary of Product Characteristics (SmPC).

If information on expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor.

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 administration, or until the start of a new antitumor therapy, whichever occurs first; 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 administration, or until the start of a new antitumor therapy, whichever occurs first:	All SAEs
From day 31 after last protocol treatment administration (or after start the start of a new antitumor therapy):	Only related SAEs

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

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 send to the EORTC Pharmacovigilance Unit:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027

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.

The investigator must provide any relevant information as requested by the Sponsor in addition to that on the CRF.

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

The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs/unexpected events to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all participating investigators whenever applicable, following the local and international regulatory requirements.

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 adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female patient diagnosed during the treatment period or within 3 months thereafter or in a female partner of a male patient diagnosed during the treatment period or within 5 months thereafter, 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 a SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter
- All neonatal deaths that occur within 30 days of birth should be reported, regardless to the causality, as SAEs. In addition, any infant death at any time thereafter that the Investigator suspects to be related to the exposure to the study drug/IMP should also be reported to the Pharmacovigilance Unit by facsimile within 24 hours of the Investigator´s knowledge of the event.

16 Quality assurance

16.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly entered 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 the inconsistencies.

16.2 On-site quality control

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

The first visit in a participating site will be performed within 6 months after the first patient's randomization at this site. Frequency and number of subsequent visits will depend on site's accrual and quality observed during the first visit.

Overall, the frequency of site visits will be around one visit a year per recruiting site.

The aim of these site visits will be:

- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of data reported on the case report forms with the source data
- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled
- 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

Retrospective central histopathology review is planned to be undertaken as a downstream translational research project, as described in the appropriate section.

16.5 External review of responses

In accordance with the recommendations of the Macdonald criteria, all responses will be reviewed by an expert or experts independent of the study.

16.6 Scan submission Quality Assurance and Quality Control in imaging

All imaging data for this trial will be centrally collected and stored, using the EORTC Imaging Platform. Sites are requested to submit the imaging data in a timely fashion manner to allow prospective QA/QC to be performed. MRI scans acquired during the trial and up to 2 years before inclusion of patients into this trial will be collected to investigate whether the growth dynamics of grade II or III meningiomas changes with start of study treatment.

In case sites are not able to transfer the imaging data electronically, the data will be sent to EORTC HQ in a CD/DVD via courier and the EORTC Imaging Team will be in charge of uploading the data on the EORTC imaging platform. Further details about the imaging data transfer can be found in the Imaging Guidelines.

The EORTC HQ will track all scans of all patients received from the sites and will request/query missing/incomplete scans. Furthermore, if the scans arrive in unacceptable quality or in a non-acceptable format, the site will be informed to provide substitute scans.

16.6.1 Imaging QA/QC level description

All documents pertaining to the Imaging QA/QC procedures will be sent to centers after receipt of the signed commitment form at the EORTC Headquarters.

The QA procedure consists of completing the following, which must be performed:

- Prior to site authorization:
  - Imaging Guidelines "read and understood" acknowledgment signature page.
  - Dummy run (DR)
- During the trial, the following imaging procedures will be performed:
  - Prospective scans QA/QC
  - Retrospective Central Review

16.6.1.1 Imaging guidelines "read and understood" acknowledgment signature page

This is the first page of the imaging guidelines. Every site participating in an EORTC study with imaging, must comply with the minimum requirements established as specified in the imaging guidelines. The first page of the imaging guidelines must be signed and returned to the EORTC HQ for every new version of the imaging guidelines. The page must be signed by the department head nuclear medicine physician and radiologist. This is mandatory from all institutions in this study before activation to participate in it.

16.6.1.2 Dummy run

Prior to enrolling patients to participate in this trial, centers are required to submit a test scan of the imaging modalities required per protocol, called dummy run (DR) scan to be reviewed by the EORTC Imaging team or its back-up, who will verify image quality, consistency of acquisition/reconstruction parameters and imaging guidelines compliance with the protocol requirements. The DR scan will not be analyzed further. For more details on DR acquisition, reconstruction and submission please refer to the Imaging Guidelines.

16.6.1.3 Prospective scan quality control

QA/QC will be performed prospectively, on an on-going basis for all imaging data collected for the trial.

The EORTC Imaging team or its back-up will be reviewing all scans for all patients to check for artifacts and to ensure compliance with the imaging guidelines and study protocol requirements. All acquisition and reconstruction parameters will be checked and recorded through the study.

Every subsequent scan on the same patient must be done with the same scanner across all visits. In case of scanner breakdown or change of scanners in the department, you need to notify the EORTC HQ.

16.6.1.4 Central review

A Blinded Independent Central Review (BICR) will be organized retrospectively to review all collected scans in this study.

The BICR will remain blinded regarding the treatment group of the patients. Furthermore, the reviewers will be blinded regarding the site's assessment which will only be unblinded to the study coordinator.

BICR ensures an independent evaluation of patient scans in a specific study by experts in the specific imaging modality. For further details about the Independent Central Review, please refer to the Central Review Charter.

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 or year of birth (as allowed per applicable legislation) 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.

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 works closely with the study team to develop the outline and full protocol and discusses the contents of the reports with the study team. The Study coordinator is responsible for publishing the study results. He/she will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

Study coordinator:

Matthias Preusser
Medical University Vienna - General Hospital AKH
Waehringer Guertel 18-20
1090 Vienna
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Phone: +43 1404004445
Fax: +43 1404004451
E-mail: matthias.preusser@meduniwien.ac.at

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

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

Brain Tumor EORTC group

Chairman:

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19 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.

20 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy” version 4.02 dated 19/03/2012.

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 final publication of associated translational research studies will be written by the Coordinator of the corresponding translational research study.

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), and the statistician and clinical research physician in charge of the trial at the EORTC Headquarters. For publication of translational research results, co-authors will also include scientific collaborators who made substantial contribution to the research.

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 data pertaining to patients from the present trial will be submitted for review to the EORTC Headquarters and to all co-authors.

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

Appendix A: References

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Appendix B: Abbreviations

AE	Adverse Event
BSA	Body Surface Area
CAV	Cyclophosphamide, Doxorubicin, and Vincristine
CI	Confidence Interval
CR	Complete Response
CTCAE	Common Toxicity Criteria Adverse Event
DNA	Deoxyribonucleic acid
HBM	Human Biological Material
HR	Hazard Ratio
MR	Minor Response
NER	Nucleotide Excision Repair
NGS	Next-generation-sequencing
OS	Overall Survival
PFS	Progression-Free Survival
PR	Partial Response
RANO	Response Assessment in Neuro-Oncology
SD	Stable Disease
WHO	World Health Organization

Appendix C: 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 D: 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 E: Calculation of the glomerular filtration rate (GFR)

COCKCROFT AND GAULT FORMULA

For the calculation of GFR age is measured in years and weight is measured in kilograms.

If serum creatinine is measured in µmol/l, the following formula applies:

In males: $GFR[ml/min] = \frac{1.23 \times (140 - age) \times weight}{serum\ creatinine}$

In females: $GFR[ml/min] = \frac{1.05 \times (140 - age) \times weight}{serum\ creatinine}$

If serum creatinine is measured in mg/dl, the following formula applies:

In males: $GFR[ml/min] = \frac{(140 - age) \times weight}{72 \times serum\ creatinine}$

In females: $GFR[ml/min] = \frac{0.85 \times (140 - age) \times weight}{72 \times serum\ creatinine}$

Appendix F: 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.

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 G: EORTC Quality of Life evaluation: guidelines for administration of questionnaires

EORTC Quality of Life evaluation: guidelines for administration of questionnaires

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?

In each institution, the principal investigator is the responsible for the local organization of QoL data collection. This can be delegated to 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 who has to complete the QOL forms and preferably without help from others. In the case where a patient is too sick to fill out the questionnaire by him/herself or if the patient is not able to complete the questionnaire for such reasons as forgetting his/her glasses, another person could read the questions without making any suggestions and report the answers on the forms. It is not allowed for another person to fill in the questionnaire as if (s)he was the patient (proxy assessment) unless specifically allowed by the protocol.

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 completing the 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 and includes date of birth and today's date (completion date)).

The following issues should be explained to the patient:

- The schedule of assessments.
- The questionnaire is a self administered questionnaire that should be completed by the patient him(her)self. The patient can ask for aid in reading or writing but should not let another person provide the answers.
- 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. The answers will not influence any medical decision making.
- All questions should be answered.
- The patient will be given a questionnaire in the default language(s) of the hospital. If desired, the patient may request another language. The RP will then contact the EORTC Headquarters for the appropriate translation.

The RP should make sure that the patient understands the instructions.

At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or from other appropriate staff if the RP is unavailable.

4. Where should the patient complete the questionnaire?

The patient should complete the questionnaire at the clinic, and, ideally in a quiet, private room. If this is not possible, the waiting room is an acceptable alternative. In general it does not take long to complete the questionnaire, but patients should be given the time they need to answer all questions.

5. When should they complete the questionnaire?

The timing of the planned QoL assessments is detailed in the protocol. 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 is to receive a therapy, the questionnaire should be filled out before administration of the treatment (unless indicated otherwise in the protocol). The questionnaire should not be taken home and/or mailed (unless indicated otherwise in the protocol).

6. Review of the completed questionnaire

After the patient has completed the questionnaire, the person handling the questionnaire should:

- Complete the "Hospital Staff" specific data box.
- Check that the completion date is correctly filled in by the patient.
- Screen the questionnaire for omissions.

If this is the case:

- Please ask the patient the reason for omissions. It may be that patient forgot to flip a page or did not understand a question. The patient should not be forced to provide an answer if (s)he does not wish to do so.
- Additional explanation may be provided, but the questions should not be rephrased.

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 the date of visit should be documented on the corresponding CRF (case report form).

8. Mailing to EORTC Headquarters

A copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. As it is impossible to retrospectively collect missing quality of life data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to complete it.

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

Quality of Life Department - EORTC Headquarters:

Phone: 32 2 774 16 61/16 06

Fax: 32 2 772 35 45

E-mail: qualityoflife@eortc.be

Appendix H: WHO classification of meningioma

Meningeal tumors	WHO grade I	WHO grade II	WHO grade III
Meningioma	•		
Atypical meningioma		•	
Anaplastic / malignant meningioma			•
Haemangiopericytoma		•	
Anaplastic haemangiopericytoma			•
Haemangioblastoma	•		

Taken from: The 2007 WHO classification of tumours of the central nervous system. Louis DN1, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. Acta Neuropathol. 2007 Aug;114(2):97-109. Epub 2007 Jul 6.

Appendix I: Local reference treatments as by national authority

The choice of the comparator in the control arm is left to the discretion of the investigator.

GERMANY:

For Germany the following drugs are considered as potential comparators by the national authority:

- [Sunitinib]
- [Carboplatin]
- [Imatinib]
- [Etoposide]

The investigator is, however, not limited to the use of these comparators.

OTHER COUNTRIES:

No other country clarifications regarding the use of comparators.